IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY

WYETH and CORDIS CORPORATION, Plaintiffs& Counterclaim Defendants vs. ABBOTT LABORATORIES and ABBOTT CARDIOVASCULAR SYSTEMS, INC. and BOSTON SCIENTIFIC CORPORATION and BOSTON SCIENTIFIC SCIMED, INC., Defendants & Counterclaim Plaintiffs	Civil Action No. 3:08-CV-00230-JAP-TJB Judge Joel A. Pisano Magistrate Judge Tonianne J. Bongiovanni
WYETH and CORDIS CORPORATION, Plaintiffs& Counterclaim Defendants vs. MEDTRONIC, INC., MEDTRONIC AVE, INC. and ABBOTT LABORATORIES, and ABBOTT CARDIOVASCULAR SYSTEMS, INC., Defendants & Counterclaim Plaintiffs	Civil Action No. 08-1021-JAP-TJB Judge Joel A. Pisano Magistrate Judge Tonianne J. Bongiovanni

OPENING MARKMAN SUBMISSION OF WYETH AND CORDIS CORPORATION

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INTRODUCTION

These actions involve three patents to Dr. Randall Morris and Dr. Clare Gregory (the "Morris patents") covering the seminal discovery that rapamycin drugs can be used to treat the re-closure of coronary arteries (called "restenosis") following an angioplasty procedure. Rapamycin drugs have been spectacularly successful in treating restenosis, have proven to be the most successful family of drugs ever used for this purpose, and are by far the most commonly used drugs on drug-eluting coronary stents in the United States today.

Coronary artery disease is the leading cause of death in the United States, and is caused by the formation of plaque which blocks the coronary artery which supplies blood to the heart. Years ago, coronary artery disease was normally treated by open heart surgery, an invasive, painful, and risky procedure in which the cardiologist opened up the patient's chest and replaced the blocked artery with a vessel from another part of the body. In 1977, cardiologists developed a technique called angioplasty, in which a balloon was inserted in a blood vessel in the leg, threaded through the vascular system to the blocked area, and inflated to open the artery by pressing the blockage into the arterial wall. (*See* Vaghani Decl. Ex. B, American Heart Association, What is Coronary Angioplasty? (2007), http://www.americanheart.org/presenter.jhtml?identifier=3009573.)[1] Angioplasty, however, suffered from a persistent problem – inflation of the balloon would often injure the cells in the arterial wall, causing them to multiply and re-block the artery. This process was known as restenosis, and was considered the Achilles heel of balloon angioplasty.

In the early 1990s, Stanford University researchers Drs. Morris and Gregory were working with Wyeth to study the use of rapamycin to prevent transplanted organs from being

[1] Copies of Exs. A-M are attached to the supporting Certificate of Savan N. Vaghani.

rejected by the body. During this work, Morris and Gregory had the unique insight that a rapamycin drug might be used to treat restenosis following a coronary angioplasty procedure. They tested their hypothesis on rats, and found that the use of a rapamycin drug did indeed inhibit restenosis. They filed patent applications on their discovery, which issued as the Morris patents at issue in this case.

The use of rapamycin drugs to treat restenosis became a huge success. Cordis used a rapamycin drug called "sirolimus" on its groundbreaking CYPHER® drug-eluting stent, the first drug-eluting stent to be tested in humans and the first to be sold in the United States. The results were spectacular. Its initial trials in humans showed virtually complete elimination of restenosis. Before that time, drug and medical device companies tried for years to solve the problem of restenosis with little success. The CYPHER® stent was approved by the Food and Drug Administration in 2003, and has had billions of dollars of annual sales since that time. After Cordis's success, others followed suit. Defendant Abbott Laboratories ("Abbott") developed a drug-eluting stent using the rapamycin drug "everolimus," which it sells as the XIENCE V® stent. Defendant Boston Scientific Corporation ("Boston Scientific") purchases the XIENCE V® stent from Abbott and sells it under the name PROMUS®. Defendant Medtronic, Inc. ("Medtronic") sells a drug-eluting stent called ENDEAVOR® which uses the rapamycin drug "zotarolimus." Three out of four of the drug-eluting stents sold in the United States today use a rapamycin drug and therefore make use of the discovery made by Drs. Morris and Gregory.

The primary claim construction dispute between the parties is the meaning of the term "rapamycin" in the claims of the Morris patents. Defendants attempt to evade the claims by limiting this term to only one specific rapamycin molecule with a particular chemical structure; their apparent aim is to exclude the virtually identical rapamycin molecules Defendants use in

their drug-eluting stents. Such an unduly narrow construction, however, is contrary to the specification and is not supported by the intrinsic evidence. Defendants also seek overly narrow constructions of several other claim terms. The Court should adopt the constructions proposed by Cordis.[2]

SUMMARY OF APPLICABLE LAW

In determining the meaning of a claim term, a court may look to intrinsic evidence, including the claim language, specification, and prosecution history, as well as extrinsic evidence. *See Phillips v. AWH Corp*., 415 F.3d 1303, 1312-19 (Fed. Cir. 2005). In reviewing this evidence, the Federal Circuit has "long emphasized the importance of the specification in claim construction." *Id.* at 1315. It is "the single best guide to the meaning of a disputed term" and is usually "dispositive." *Id.* In particular, where the specification reveals "a special definition given to a claim term by the patentee," the "inventor's lexicography governs." *Id.* at 1316. It is improper, however, to limit the claims to specific embodiments set forth in the specification. *Id.* at 1323.

The Federal Circuit has also noted that "[i]n addition to consulting the specification," a court "should also consider the patent's prosecution history, if it is in evidence." *Id.* at 1317. The Federal Circuit has recognized, however, that "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and is thus less useful for claim construction purposes." *Id.* Where a party alleges that the inventors limited their claims by

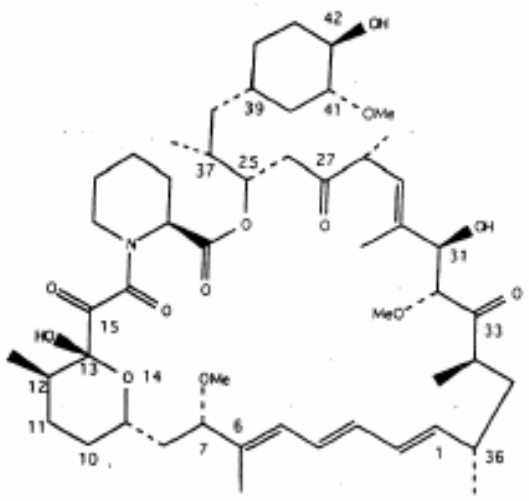
[2] The parties have reached agreement on two terms previously in dispute – "treating" and "preventing." The parties have agreed that the term "treating" should be construed to mean "retarding the progression of, arresting the development of, or palliating [restenosis / hyperproliferative vascular disease]." The parties have agreed that the term "preventing" restenosis should be construed to mean "inhibiting the development of or prophylactically preventing restenosis."

making statements in the prosecution history, it must show that "the allegedly disclaiming statements constitute 'a clear and unmistakable surrender of subject matter.'" *Ecolab, Inc. v. FMC Corp.*, 569 F.3d 1335, 1342 (Fed. Cir. 2009) (citation omitted).

A court may also consider extrinsic evidence, which includes "all evidence external to the patent and prosecution history, including expert and inventor testimony, dictionaries, and learned treatises." *Phillips*, 415 F.3d at 1317. However, "while extrinsic evidence 'can shed useful light on the relevant art,'" it is "less significant than the intrinsic record in determining the legally operative meaning of claim language." *Id.* (citation omitted).

ARGUMENT

I. "RAPAMYCIN"

"rapamycin"	
Cordis's Proposed Construction	**Defendants' Proposed Construction**
a compound containing a macrocyclic triene ring structure produced by *Streptomyces hygroscopicus*, having immunosuppressive and anti-restenotic effects	the chemical compound produced by *Streptomyces hygroscopicus* which has the following structure: 

The term "rapamycin" is found in every asserted claim of the Morris patents. (*See, e.g.*, Danishefsky Decl. Ex. 6, U.S. Patent No. 5,516,781 (hereinafter "'781 Patent"), Claim 1.)[3] The intrinsic evidence supports Cordis's proposed construction, which is based on the specification of the Morris patents.

A. Background

1. The Discovery of Rapamycin

The history of rapamycin traces back to a soil sample collected decades ago on Easter Island, a remote Pacific island 2000 miles off the coast of Chile. (Danishefsky Decl. ¶ 15.) In the mid 1970s, Dr. Surendra Sehgal, a scientist at the Ayerst Research Laboratories (which later became part of plaintiff Wyeth), discovered that a culture of a particular strain of the bacterium *Streptomyces hygroscopicus*, isolated from a soil sample collected from Easter Island, exhibited antifungal activity. (*Id.*) The fermentation product of the bacterium containing the active material was isolated and named "rapamycin," after the Polynesian name for Easter Island, Rapa Nui. (*Id.*)

Originally, neither the structure of rapamycin nor its biological effects were fully understood. The term "rapamycin" was originally applied to the fermentation product of the bacterium *Streptomyces hygroscopicus* that showed antifungal activity, rather than to a particular compound of known structure. (Danishefsky Decl. ¶ 13.) The use of a name to refer to a family of compounds based on a naturally-produced drug was common in the antibiotics field. (Danishefsky Decl. ¶ 14.) When scientists discover a new naturally produced drug, there is an expectation that other researchers will attempt to make small chemical modifications to try to alter or improve particular characteristics, while retaining the core structure and therefore the

[3] The three patents in suit, U.S. Patent No. 5,516,781, U.S. Patent No., 5,563,146 and U.S. Patent No. 5,665,728 share a common specification.

desired biological activities of the natural compound. (*Id*.) A classic example is "penicillin," which refers to any of a group of antibiotic compounds obtained from *Penicillium* molds or produced synthetically. (*Id*.)

In their initial studies, Dr. Sehgal and his colleagues at Ayerst examined the physical and chemical properties of "rapamycin" and, based on its ultraviolet spectrum, classified it as belonging to the class of antibiotics known as triene antibiotics, so named because they included three adjacent carbon-carbon double bonds, called a "triene." (Danishefsky Decl. ¶ 16.) The Ayerst researchers, however, did not know and did not provide the chemical structure for what constituted "rapamycin," or otherwise limit it to a single chemical entity. (*Id*.) None of the physical and chemical characteristics of "rapamycin" determined in these initial studies provided sufficient information to exclude other closely related compounds from "rapamycin." (*Id*.) Indeed, because the fermentation products of *Streptomyces hygroscopicus* contain several closely related compounds, even crystalline antibiotic samples of "rapamycin" may contain other compounds. (*Id*.)

Between the late 1970s and the early 1990s, researchers conducted structural analyses of the active material produced by *Streptomyces hygroscopicus*, which revealed the chemical structure of one naturally-produced compound. (Danishefsky Decl. ¶ 17.) The structure of this specific rapamycin was first published in 1978, with a more detailed structural diagram published in 1981. (*Id*.) In 1993, this specific "rapamycin" was assigned the name "sirolimus" by the United States Adopted Names Council, which is a body that selects nonproprietary names for drugs marketed in the United States. (Danishefsky Decl. ¶¶ 18, 39.)

2. The Biological Activity of Rapamycin

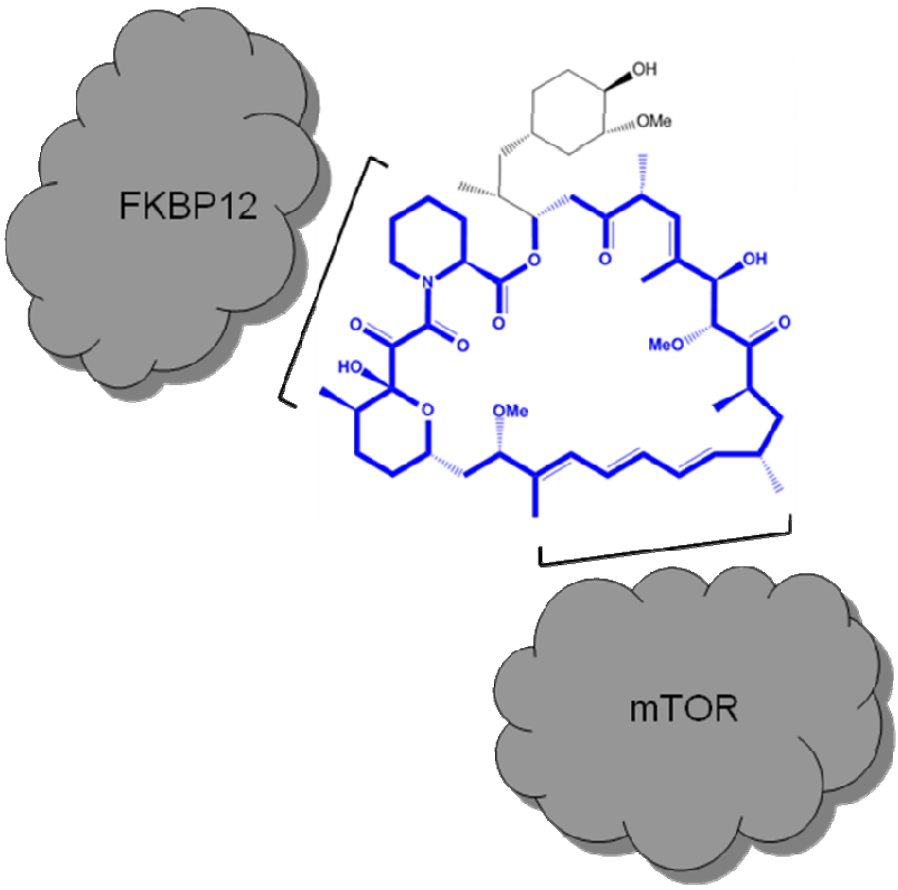
When rapamycin was first discovered, the Ayerst researchers found that it exhibited powerful antifungal activity, particularly against the yeast *Candida albicans*, which can cause

yeast infections. (Danishefsky Decl. ¶ 15.) Over time, they discovered that rapamycin had other biological properties, including antitumor effects and suppression of the immune system. (*Id*.) Although these immunosuppressive properties were originally viewed as problematic, researchers working with American Home Products (which also became part of Wyeth) found that rapamycin could be successfully used to treat the rejection of transplanted organs, and developed it into a successful drug, RAPAMUNE®, for that purpose. (Vaghani Decl. Ex. A, Rapamune Prescribing Information.)

One of the scientists collaborating with Wyeth on the use of rapamycin for transplant rejection was Dr. Randall Morris of Stanford University. In the course of his research, Dr. Morris, along with his colleague Dr. Clare Gregory, had the insight that rapamycin might be useful in treating the reclosure of arteries that occurs following a coronary angioplasty procedure. Drs. Morris and Gregory tested this hypothesis, and discovered that rapamycin did in fact inhibit restenosis in a rat model. A rapamycin (sirolimus) was ultimately selected by Cordis for use in the ground-breaking CYPHER® drug-eluting stent, which was the first drug-eluting stent approved by the FDA and which finally solved the long-standing problem of restenosis. Drs. Morris and Gregory filed patent applications on their discovery, which ultimately resulted in the patents-in-suit in this action.

3. The Mechanism of Action of Rapamycin

Rapamycin has a unique mechanism of action that is responsible for its biological activity in suppressing the immune system and inhibiting restenosis. When introduced into the body, rapamycin binds to a protein known as FKBP-12. (Danishefsky Decl. ¶¶ 19-20.) The rapamycin/FKBP-12 complex then binds to another protein called the mammalian target of rapamycin, or mTOR. (Danishefsky Decl. ¶ 21-22.) The binding regions of FKBP12 and mTOR are shown below:



(Danishefsky Decl. ¶ 22.) Because the binding of FKBP-12 and mTOR takes place on the macrocyclic ring of the parent compound (bolded and colored in blue in the diagram above), scientists recognized that this ring structure was important to the function of the drug. (Danishefsky Decl. ¶ 19.) The macrocyclic ring also contains the triene portion of the molecule, which was also considered to play an important role in its structure and function. (Danishefsky Decl. ¶ 22.)

Through this binding mechanism, rapamycin slows or stops cell proliferation by blocking the transition of smooth muscle cells from G1 to S phase of the cell cycle.[4] (Danishefsky Decl.

[4] The cell cycle is the process by which cells multiply. It is an ordered sequence of events in which a cell duplicates its genetic material (or DNA) and divides into two daughter cells. The cell cycle of mammalian cells can be divided into four phases. The phase prior to the duplication of genetic material (or S phase) is called the G1 phase (the first gap). G1 gives way to the S

(Footnote continued)

¶¶ 19, 21.) By interfering with the reproduction of smooth muscle cells, rapamycin reduces the narrowing of the artery caused by the proliferation of smooth muscle cells. (Danishefsky Decl. ¶ 37.)

4. Rapamycin Compounds

When scientists discover a new naturally produced drug or compound of interest, it is common practice to tinker with its basic structure to try to alter or improve it. (Danishefsky Decl. ¶ 14.) Slight chemical modifications can be made to try to alter or improve particular characteristics, while retaining the mechanism of action and biological activity of the naturally-produced molecule. (*Id*.)

This practice was carried out with the parent rapamycin compound, sirolimus. Different investigators made a variety of modifications to the parent rapamycin structure produced by the *Streptomyces hygroscopicus* bacterium, and explored the effect of these modifications on biological activity. (Danishefsky Decl. ¶¶ 42-53.) Two compounds that were developed in this way – called everolimus and zotarolimus – are used on the accused products in this case. Everolimus is used on the Abbott XIENCE V® stent and the Boston Scientific PROMUS® stent, while zotarolimus is used on the Medtronic ENDEAVOR® stent. (Danishefsky Decl. ¶¶ 47, 52.) Both everolimus and zotarolimus were produced by culturing the *Streptomyces hygroscopicus* bacterium to produce sirolimus, and then making slight chemical modifications at the region of the sirolimus molecule that is shown below in the upper right. No changes were made to the critical macrocyclic ring structure where the binding to FKBP-12 and mTOR takes

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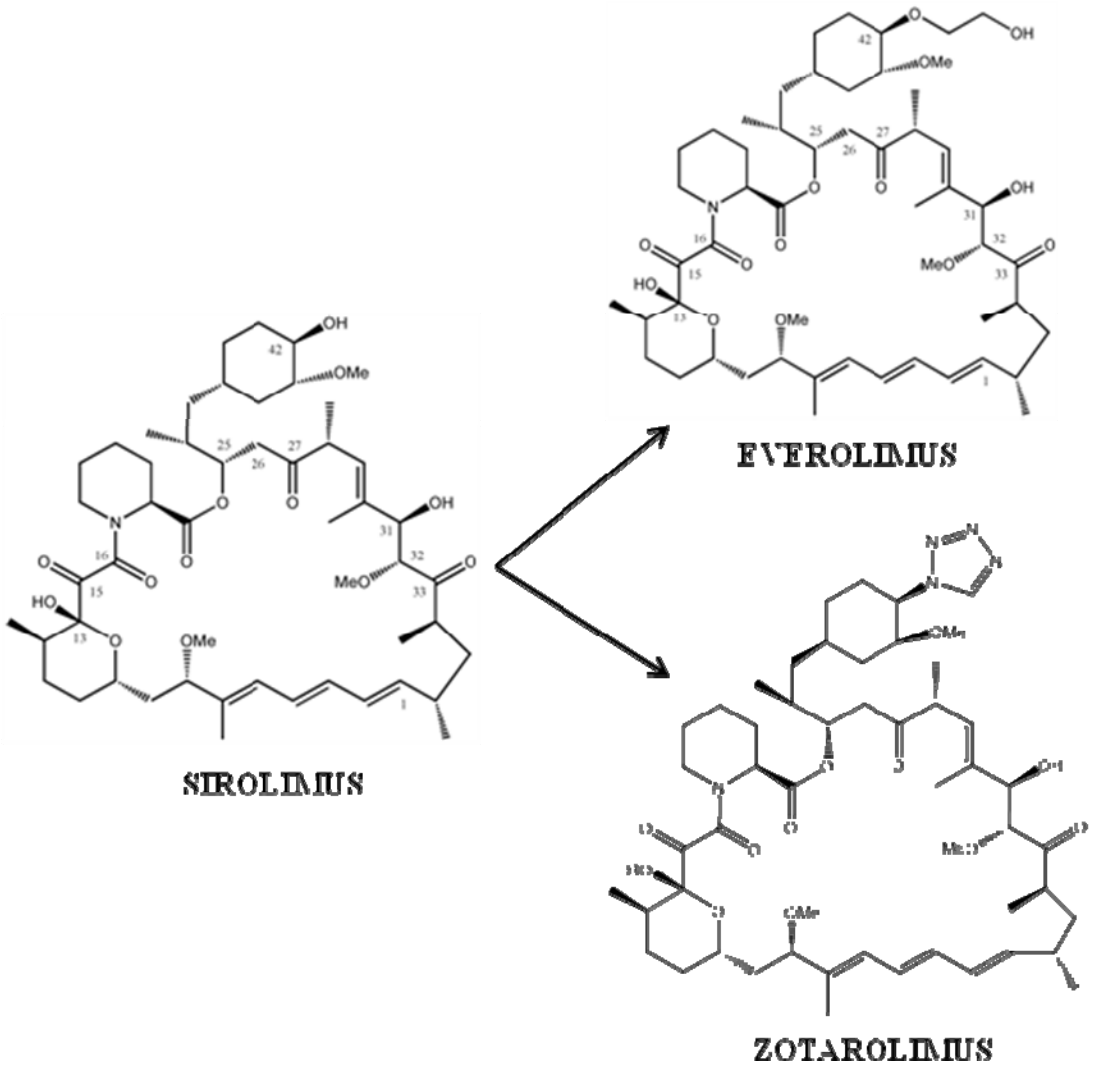
phase (for synthesis), during which the cell duplicates its genetic material. The S phase is followed by the G2 phase (the second gap). The cell cycle then culminates in cell division through a process called mitosis or M phase. Progression through the various phases of the cell cycle is regulated by the synthesis, activation, and degradation of specific proteins. (*See generally* Danishefsky Decl. Ex. 24, Lodish *et al.*, MOLECULAR CELL BIOLOGY (W.H. Freeman and Company, 2d ed. 1990) at pp. 151-188.)

place. (Danishefsky Decl. ¶¶ 42-46, 49-51.) The structures of three rapamycins, sirolimus, everolimus and zotarolimus, are shown below:



The slight modifications of the sirolimus molecule that result in everolimus and zotarolimus do not interfere with the mechanism of action and essential biological activity of the parent compound because the macrocyclic ring structure that is produced by the bacterium and that is critical to binding to FKBP-12 and mTOR (as shown in the illustration on page 8 above) is unchanged. (Danishefsky Decl. ¶ 46, 51.) All three molecules bind to FKBP-12 and mTOR. (Danishefsky Decl. ¶¶ 48,53.) All three interrupt cell replication at the G1-S phase. (*Id.*) All

three inhibit neointimal proliferation and restenosis. (Danishefsky Decl. ¶¶ 47, 52.) All three have been successfully used on a stent to treat restenosis. (*Id*.) Because they are rapamycin drugs, these compounds have been referred to as "rapamycin" or "rapamycins." (Danishefsky Decl. ¶¶ 42, 49.)

B. The Evidence Supports Cordis's Proposed Construction

1. The Specification of the Morris Patents Defines "Rapamycin" as a Compound Containing a Macrocyclic Triene Ring Structure Produced by *Streptomyces Hygroscopicus* Having Immunosuppressive and Anti-Restenotic Effects.

As the Federal Circuit has explained, the specification "is the single best guide to the meaning of a disputed term," and is usually "dispositive." *Phillips*, 415 F.3d at 1315. The specification "is, thus, the primary basis for construing the claims." *Id.* The specification "acts as a dictionary when it expressly defines terms used in the claims or when it defines terms by implication." *Id.* at 1321.

Cordis's proposed construction ("a compound containing a macrocyclic triene ring structure produced by *Streptomyces hygroscopicus*, having immunosuppressive and anti-restenotic effect") is based on language in the specification of the Morris patents. The specification describes "rapamycin" in Column 3 as follows:

> ***Rapamycin, a macrocyclic triene antibiotic produced by Streptomyces hygroscopicus*** [U.S. Pat. No. 3,929,992] has been shown to prevent the formation of humoral (IgE-like) antibodies in response to an albumin allergic challenge [Martel, R., *Can. J. Physiol. Pharm.* 55:48 (1977)], inhibit murine T-cell activation [Staruch, M., *FASEB* 3:3411 (1989)], prolong survival time of organ grafts in histoincompatible rodents [Morris, R., *Med. Sci. Res.* 17:877 (1989)], and inhibit transplantation rejection in mammals [Calne, R., European Patent Application 401,747]. Rapamycin blocks calcium-dependent, calcium-independent, cytokine independent and constitutive T and B cell division at the G1-S interface. Rapamycin inhibits gamma-interferon production induced by n-1 and also inhibits the gamma-interferon induced expression of membrane antigen. [Morris, R. E., *Transplantation*

> *Rev*. 6:39 (1992)]. The use of rapamycin in preventing coronary graft atherosclerosis (CGA) in rats has been disclosed by Meiser [*J. Heart Lung Transplant* 9:55 (1990)]. Arterial thickening following transplantation, known as CGA, is a limiting factor in graft survival that is caused by a chronic immunological response to the transplanted blood vessels by the transplant recipient's immune system. [Dec. G, *Transplantation Proc.* 23:2095 (1991) and Dunn, M. *Lancet* 339: 1566 (1992)].

(Danishefsky Decl. Ex. 6, '781 Patent at 3:1-24. (emphasis added).)

From this portion of the specification, a person of ordinary skill would understand "rapamycin" to have several characteristics. First, the specification describes rapamycin by its structure as "a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*." (Danishefsky Decl. ¶ 34.) From this, a person of skill in the art would understand "rapamycin" to be a "macrocyclic triene antibiotic." (*Id*.) A person of skill in the art would also understand the macrocyclic triene structure in question to be the one that is produced by a particular bacterium – *Streptomyces hygroscopicus*. (*Id*.)

A person of skill in the art reading the specification would further understand that a rapamycin, as the term is used in the specification, has immunosuppressive effects. (Danishefsky Decl. ¶ 36.) The balance of the paragraph quoted above recites specific properties of a rapamycin, each of which is an immunosuppressive activity. (*Id*.) From this description, a person skilled in the art would understand that "rapamycin" has immunosuppressive activity. (*Id*.)

In addition to immunosuppressive activity, the specification further explains that a rapamycin, as the term is used in the specification, inhibits restenosis, and therefore has anti-restenotic effects, stating that:

> The effect of rapamycin on hyperproliferative vascular disease was established in an in vitro and in vivo standard pharmacological test procedure that emulates the hyperproliferative effects observed in

> mammals that are undergoing intimal smooth muscle proliferation and are therefore developing restenosis.

(Danishefsky Decl. Ex. 6, '781 Patent at 4:23-28.) (*See also id.* at 3:45-10:16.) The specification then describes several *in vitro* laboratory experiments showing that rapamycin inhibited smooth muscle proliferation (a key factor in restenosis) (*Id.* at 4:33- 6:2; Danishefsky Decl. ¶ 37) and *in vivo* experiments in rats showing that rapamycin inhibited actual restenosis following arterial injury. (Danishefsky Decl. Ex. 6, '781 Patent at 6:3-10:17; Danishefsky Decl. ¶ 37.) From this description in the specification, a person skilled in the art would understand that "rapamycin" has anti-restenotic effects. (Danishefsky Decl. ¶ 37.)

Cordis's proposed construction of "rapamycin" is therefore a succinct shorthand for the specification's detailed description of what "rapamycin" is. (Danishefsky Decl. ¶ 32.)

2. Cordis's Proposed Construction Is Consistent With the Ordinary Meaning of the Term in 1992 as Used by the Inventors and Others in the Field.

Cordis's proposed construction is also consistent with the way the term "rapamycin" was used by inventors Morris and Gregory and by others in the field at the time the patent application was filed. Prior to the filing of the patents-in-suit, the inventors and others in the field used the term "rapamycin" or "rapamycins" to refer to rapamycin drugs. [redacted] In January 1992, at about the same time that the initial patent application was filed, Morris published an article in the peer-reviewed Journal *Transplantation* entitled "***Rapamycins***: Antifungal, Antitumor, Antiproliferative, and Immunosuppressive Macrolides." (Danishefsky Decl. Ex. 14. (emphasis added).) Cordis's expert, Professor Samuel Danishefsky of Columbia University, also states that the term "rapamycin" is used to refer to the

molecules containing the basic ring structure produced by *Streptomyces hygroscopicus* and having the same mechanism of action and biological activity. (Danishefsky Decl. ¶¶ 12, 32, 35.)

To this day, the terms "rapamycin" and "rapamycins" continue to be used to describe rapamycin drugs. (Danishefsky Decl. ¶ 12.) For example, a recent article in the journal *Cardiovascular Research* described everolimus as "rapamycin." (Danishefsky Decl. Ex. 9, Nührenberg *et al.*, EMAP-II downregulation contributes to the beneficial effects of rapamycin after vascular injury, *Cardiovascular Research* 2008;77:580-589.) Another article in the journal *Cancer Cell* also referred to everolimus (RAD-001) and two other modifications (temsirolimus (CCI-779) and deforolimus (AP-23573)) as rapamycin. (Danishefsky Decl. Ex. 11, Guertin *et al.*, Defining the Role of mTOR in Cancer, *Cancer Cell* 2007;12:9-22 at 15 (describing temsirolimus (CCI-779), everolimus (RAD-001) and deforolimus (AP-23573) as "rapamycin").) (*See also* Danishefsky Decl. Ex. 10, Dancey, J. E., Inhibitors of the mammalian target of rapamycin, *Expert Opin Investig Drugs* 2005;14(3):313-328 at 313,316-323 (describing the mTOR inhibitors temsirolimus (CCI-779), everolimus (RAD-001), and deforolimus (AP-23573) as "rapamycins," and referring to deferolimus as "rapamycin"); Danishefsky Decl. Ex. 12, Huang *et al.*, Rapamycins: Mechanism of Action and Cellular Resistance, *Cancer Biology & Therapy* 2003; 2:222-232 at 222-223 (describing "rapamycins"); Danishefsky Decl. Ex. 13, Huang *et al.*, Mechanisms of resistance to rapamycins, *Drug Resistance Updates* 2001;4:378-91 ("Huang (2001)") at 378 (describing "rapamycins").)

3. The Prosecution History Is Consistent With Cordis's Proposed Construction.

A court "should also consider the patent's prosecution history, if it is in evidence." *Phillips*, 415 F.3d at 1317. However, "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation,

it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Id.* As a result, "unclear prosecution history cannot be used to limit claims." *Cordis Corp. v. Boston Scientific Corp.*, 561 F.3d 1319, 1329 (Fed. Cir. 2009).

Here, the prosecution history is consistent with Cordis's proposed construction. During the prosecution history, the examiner rejected the pending claims (then numbered 5 and 7-10) for obviousness-type double patenting based on two other Wyeth patents that involved changes to the macrocyclic triene ring of rapamycin, U.S. Patent Nos. 5,252,579 (the " '579 patent") and 5,256,790 (the " '790 patent"). (Vaghani Decl. Ex. D, June 26, 1995 Office Action in Application No. 08/239,305.) The applicants responded to the rejection by explaining that in the compounds described in the '579 and '790 patents, the macrocyclic triene ring structure produced by *Streptomyces hygroscopicus* had been intentionally modified, and the "rapamycin" claimed in the pending application did not have changes of this kind to the macrocyclic ring. (Vaghani Decl. Ex. E, Sept. 22, 1995 Response in Application No. 08/239,305.)

For instance, with reference to the '579 patent, the applicants stated that "the oxygen in the 24-position of rapamycin has been replaced by X . . . . The 24-position of the compound covered by the applicants' claims is oxygen." (Vaghani Decl. Ex. E at pp. 1-2.) Because the 24-position is on the macrocyclic triene ring of rapamycin, the '579 patent significantly modifies the macrocyclic ring at this position by breaking it open and adding long chains of attached carbons, nitrogens, rings, etc. (Danishefsky Decl. ¶¶ 54-56.) This has a significant impact on the structure and size of the macrocyclic ring, which is the portion of the molecule critical for binding to FKBP-12 and mTOR. (Danishefsky Decl. ¶ 56.) Thus, the compounds claimed in the '579 patent do not contain a macrocyclic triene ring structure produced by *Streptomyces hygroscopicus*. (Danishefsky Decl. ¶¶ 54-56.)

Similarly, in connection with the '790 patent, the applicants overcame the examiner's objections by noting that "[t]he compound covered by the applicants' claims has a ketone at the 27-position, whereas all the compounds embraced by Claim 10 of U.S. Patent 5,256,290 [sic, 790] contain an esterified hydroxyl group at the 27-position." (Vaghani Decl. Ex. E at p. 2.) The 27-position is also on the macrocyclic triene ring of rapamycin. (Danishefsky Decl. ¶¶ 57-59.) The modification there changes the structure and size of the macrocyclic ring, which is critical for binding to FKBP-12 and mTOR. (Danishefsky Decl. ¶ 59.) Thus, as with the '579 patent, the compound claimed in the '790 patent does not contain a macrocyclic triene ring structure produced by *Streptomyces hygroscopicus*. (Danishefsky Decl. ¶¶ 57-59.)

C. Defendants' Proposed Construction of "Rapamycin" Is Not Supported by the Specification, Is Unduly Narrow, and Would Confuse the Jury

Defendants' construction of "rapamycin" attempts to limit the term to a single molecule defined by a particular chemical structure diagram, as depicted in their proposed construction above. The molecule is sirolimus. (Danishefsky Decl. ¶ 39.) The chemical structure of sirolimus is not disclosed in the claims, specification, or prosecution history of the Morris Patents. In fact, no chemical structures of any kind are disclosed.

Nowhere in the specification did the inventors limit "rapamycin" to a single chemical structure. By the time the application for patents-in-suit was filed in January of 1992, the chemical structure of the parent compound had been known for over 10 years, having been published in the scientific literature in 1981. (Danishefsky Decl. ¶ 17; Danishefsky Decl. Ex. 14 at p. 45; Danishefsky Decl. Ex. 21, White *et al.*, The Structure of the Antifungal Antibiotic Rapamycin, *Crystallography in Biochemistry and Pharmacology* 1981;C75.) If the inventors wanted to define rapamycin in terms of this chemical structure, they could have easily done so by either reproducing the chemical structure in the specification or citing the scientific paper that

contained a detailed description of the structure. They did not do so. Instead, they described "rapamycin" more broadly as "a macrocyclic triene antibiotic produced by *Streptomyces hygroscopicus*" having particular biological activity (immunosuppressive and anti-restenotic). The Court should not substitute a chemical structure diagram of a single compound for the broader definition the inventors themselves chose to use.

The prosecution history also fails to limit the term "rapamycin" to the particular chemical structure set forth in Defendants' proposed construction. Although the applicants distinguished certain compounds that had changes to the "macrocyclic" ring, they did not limit the invention to a particular chemical structure or disclaim other variations to that structure. As the Federal Circuit has explained, "we will find that the applicant disclaimed protection during prosecution only if the allegedly disclaiming statements constitute 'a clear and unmistakable surrender of subject matter.'" *Ecolab, Inc.*, 569 F.3d at 1342 (citation omitted); *Cordis Corp*, 561 F.3d at 1329 ("[a] disclaimer must be 'clear and unmistakable,' and unclear prosecution history cannot be used to limit claims"). There was no such "clear and unmistakable" disclaimer here that would limit "rapamycin" to the chemical structure for the single compound set forth in Defendants' proposed construction.

Construing "rapamycin" in textual fashion (*i.e.*, in words) is also likely to be more helpful to the jury than providing them with a diagram of a complex molecule that the average juror would find difficult to understand. This is particularly true because the claim construction is typically read to the jury in the form of a jury instruction.

In short, there is no basis to depart from the textual description of "rapamycin" provided by the inventors in the Morris patent specification, and the Court should not adopt Defendants'

invitation to construe "rapamycin" as constituting an illustration of a chemical structure for a single compound that is not disclosed in the specification or prosecution history.

II. "IMPREGNATED"

"impregnated"	
Cordis's Proposed Construction	**Defendants' Proposed Construction**
filled, imbued, mixed, furnished, or saturated or filled, imbued, mixed, furnished, saturated, diffused, or permeated with another substance	diffused, saturated, or permeated with another substance

The asserted claims of the Morris Patents all provide that rapamycin may be administered "via a vascular stent impregnated with rapamycin." (*See, e.g.*, Danishefsky Decl. Ex. 6, '781 Patent, Claim 1.) As reflected in the 1993 edition of *Webster's Third New International Dictionary of the English Language*, the ordinary meaning of the term "impregnated" is "to cause to be filled, imbued, mixed, furnished, or saturated." (Vaghani Decl. Ex. F, *Webster's Third New International Dictionary of the English Language* (Unabridged) 1136 (1993).)

Nothing in the specification or the prosecution history limits the ordinary meaning of the term "impregnated" in the claims. The specification merely states broadly that rapamycin may be given to the patient by "administering" it "via a vascular stent impregnated with rapamycin." (Danishefsky Decl. Ex. 6, '781 Patent, 3:47-50; 11:40-44.) There is no limitation or restriction on how the drug is to be loaded onto the stent. Accordingly, Cordis proposes using the ordinary meaning of "impregnated."

Defendants' proposed construction omits some of the broadening elements of the standard definition of "impregnate" – namely, "filled," "imbued," "mixed," and "furnished." There is no support in the intrinsic evidence for narrowing the definition of "impregnate" in this fashion.

Defendants' proposed construction adds some additional descriptors for the term "impregnated," specifically "diffused," "saturated," and "permeated." Cordis believes that these are also permissible uses of the term "impregnated," and has no objection to adding them to the construction of impregnated. Accordingly, Cordis has provided above alternative constructions of "impregnated" that either omit or employ these added descriptors.

III. "PARENTERALLY"

"parenterally"		
Cordis's Proposed Construction	**Abbott and Medtronic's Proposed Construction**	**BSC's Proposed Construction**
other than by way of the intestines	systemic administration of a substance by injection given either intravenously, intra-arterially, subcutaneously, intramuscularly, or intraperitoneally	systemic administration of a substance by means other than through the gastrointestinal tract, in particular via intravenous, subcutaneous, intramuscular, or intramedullary injection

The asserted claims of the Morris Patents all provide that rapamycin may be administered "parenterally." (*See, e.g.*, Danishefsky Decl. Ex. 6, '781 Patent, Claim 1.) The ordinary meaning of the term "parenterally" is "other than by way of the intestines" as reflected by the following dictionary definitions:

> Parenteral: "entering the body by some means other than the intestine." (*Academic Press Dictionary of Science and Technology* 1576 (1992), Vaghani Decl. Ex. G.)
>
> Parenteral: "situated or occurring outside the intestine, *esp:* introduced otherwise than by way of the intestines." (*Merriam-Webster's Collegiate Dictionary* 844 (10th ed. 1993), Vaghani Decl. Ex. H.)

> Parenteral: "involving the introduction of a substance into the body other than by the alimentary tract." (*Oxford English Dictionary Online* (2009), Vaghani Decl. Ex. I.)
>
> Parenteral: "outside the intestine; not via the alimentary tract." (*McGraw-Hill Dictionary of Scientific and Technical Terms* 1449 (5th ed. 1994), Vaghani Decl. Ex. J.)

Cordis's proposed construction reflects the ordinary meaning of the term.

Defendants' proposed constructions of "parenterally" are inconsistent with this ordinary meaning. As is clear from the definitions above, "parenteral" administration does not require a "systemic" administration or an administration that is "by injection," both of which appear to be required in Defendants' proposals. Moreover, there is nothing in the claims, specification, or prosecution history that indicates that the applicants intended the special definition of "parenteral" that Defendants advocate.

The lack of any intrinsic support for Defendants' proposed constructions is highlighted by the fact that Defendants themselves cannot agree on a uniform construction for the term. BSC's proposed construction requires "systemic" administration, but does not appear to require administration by injection. The proposed construction offered by Abbott and Medtronic, by contrast, requires injection. The fact that the defendants cannot agree highlights the fact that there is nothing in the claim language, specification, or prosecution history that would clearly redefine the term "parenterally" in a manner different from its ordinary meaning.

IV. THE "EFFECTIVE AMOUNT" LIMITATIONS

"antirestenosis effective amount"	
Cordis's Proposed Construction	**Defendants' Proposed Construction**
an amount that is capable of reducing the incidence or degree of restenosis	to the extent not indefinite: an amount sufficient to stop or significantly reduce restenosis
"antiproliferative effective amount"	
Cordis's Proposed Construction	**Defendants' Proposed Construction**
an amount that is capable of reducing the incidence or degree of cell proliferation	to the extent not indefinite: an amount sufficient to stop or significantly reduce cell proliferation[5]

Claims 1 and 2 of the '781 Patent and Claim 1 of U.S. Patent No. 5,563,146 require the administering of an "antirestenosis effective amount" of rapamycin. Claim 2 of U.S. Patent No. 5,665,728 requires the administering of an "antiproliferative effective amount" of rapamycin. Cordis contends that an "effective amount" is an amount capable of reducing restenosis (or cell proliferation). Defendants, however, insist that any reduction must be significant.

The ordinary meaning of the term "effective" is "capable of bringing about an effect." (*Webster's Third New International Dictionary of the English Language* (Unabridged) 724 (1993), Vaghani Decl. Ex. F.)[6] The ordinary meaning of an "anti-restenosis *effective* amount" is therefore an amount that is capable of bringing about an effect in countering restenosis. Similarly, the ordinary meaning of an "anti-proliferative *effective* amount" is an amount that is

[5] On November 3, 2009, Defendants altered their proposed construction of the "effective amount" limitations to the definitions listed here. Previously, in the Joint Claim Construction Statement, Defendants' defined "antirestenosis effective amount" as "to the extent not indefinite: an amount sufficient to stop restenosis" and "antiproliferative effective amount" as "to the extent not indefinite: an amount sufficient to stop cell proliferation." (Vaghani Decl. Ex. K, Joint Claim Construction Statement at pp. 4, 5.)

[6] *See also Dorland's Illustrated Medical Dictionary* 531 (28th ed. 1994), Vaghani Decl. Ex. L (defining "effectiveness" as "the ability to produce a specific result or to exert a specific measurable influence"); *American Heritage Dictionary of the English Language* at 587 (3d ed. 1992), Vaghani Decl. Ex. M (defining "effective" as "having an intended or expected effect").

capable of bringing about an effect in countering cell proliferation. Cordis's proposed constructions are consistent with this ordinary meaning.

Defendants' proposed constructions, which add the term "significantly," are not supported by the intrinsic evidence. To begin with, the claim language merely states that the amount used must be "effective," not that it must produce a "significant" effect. If the inventors had intended to impose such a requirement, they could have easily said so in the claim. Additionally, neither the specification nor the prosecution history define the term "effective" in a manner narrower than or contrary to its ordinary meaning. To the contrary, the specification merely states that the "antiproliferative effective amount" of rapamycin is useful for "preventing or treating hyperproliferative vascular disease in a mammal." (Danishefsky Decl. Ex. 6, '781 Patent at 3:45-50.) Cordis's proposed construction is therefore the correct one.

V. "STENT"

"stent"	
Cordis's Proposed Construction	**Defendants' Proposed Construction**
a tubular device for placement in a vessel, such as a coronary artery, to treat or prevent a narrowing of that vessel	a device for providing support for a lumen in the body

The patents-in-suit all disclose and claim the use of a "vascular stent impregnated with rapamycin." (*See, e.g.*, Danishefsky Decl. Ex. 6, '781 Patent at 3:45-50, 11:40-44, Claim 1.) The specification of the Morris patents as well as the nature of the invention make it clear that the claimed stent is a device for placement in a vessel to treat or prevent a narrowing of that vessel. The very first sentence of the specification explains that the invention is directed to "individuals" that "suffer from heart disease caused by a partial blockage of the blood vessels that supply the heart with nutrients." (Danishefsky Decl. Ex. 6, '781 Patent at 1:14-18.) The specification further explains that the invention, including the claimed stent, "provides a method of preventing

or treating hyperproliferative vascular disease in a mammal." (*Id.* at 3:45-50.) The specification later explains that the claimed stent is used "during balloon catheterization," which is a procedure to open up a blood vessel clogged by plaque. (*Id.* at 11:40-44.)

Defendants' proposed construction provides a more generalized definition of the term "stent" which is not restricted to blood vessels or to devices used to treat or prevent a narrowing of a blood vessel. Cordis's proposed construction, which takes into account the context and purpose of the invention set forth in the specification, is more respectful of the intrinsic evidence and should be adopted.

CONCLUSION

For the foregoing reasons, Cordis respectfully requests that its proposed constructions be adopted.

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